The Efficacy of Transarterial Chemoembolization in Downstaging Unresectable Hepatocellular Carcinoma to Curative Therapy: A Predicted Regression Model

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Research

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Abstract

Background: Patients with hepatocellular carcinoma (HCC) outside the Milan criteria (MC) may be candidates for curative therapy after successful downstaging. However, there have been no studies that have examined the factors affecting the efficacy of transarterial chemoembolization (TACE) on downstaging. We aimed to identify the predictors of successful downstaging of unresectable HCC in patients by TACE outside the MC.

Methods: We performed a retrospective study on patients with unresectable HCC outside the MC who received downstaging with TACE. Clinical and laboratory variables were recorded. We identified 101 patients with unresectable HCC who underwent initial TACE, and they formed the derivation set of this study. Thirty patients who received TACE treatment with the same selection criteria served as an external validation set. We performed multivariate logistic regression analyses to identify the variables associated with successful downstaging. Then, we created a predictive model and determined its accuracy in predicting the efficiency of TACE.

Results: Of the 101 patients in the study, 26 patients (25.7%) were successfully downstaged. Multivariate analysis was performed on the number of tumors (P=0.018), portal vein tumor thrombi (PVTT) (□0.001), the size of tumors (P=0.021), hepatitis B surface antigen (HBsAg) (P=0.014), and a-fetoprotein (AFP, P=0.027), which were considered as significant predictors of successful downstaging of HCC outside the MC. Then, we constructed the predictive model. The area under the ROC curve (AUROC) for the predictive equation was 0.908 (95% confidence interval, 0.832-0.957).

Conclusions: We found in our study that the number and size of tumors, PVTT, HBsAg, and AFP are good predictors of successful downstaging of unresectable HCC in patients by TACE outside the MC.

Introduction

Primary liver cancer is the second most frequent cause of cancer death worldwide, with hepatocellular carcinoma (HCC) representing the most common form of primary liver cancer.[1] This highly malignant tumor portends a median survival of □1 year without treatment. [2] A variety of treatment options are available to HCC patients depending on the number of patient and tumor characteristics.[1] Currently, curative treatments such as surgical resection and liver transplantation are the most optimal treatments for HCC. Unfortunately, almost 80% of patients with HCC are initially diagnosed at the intermediate or advanced stage, and hence are ineligible for curative treatment.[3]

For patients with unresectable HCC, downstaging is attempted to bring tumors within the Milan criteria (MC) (a single nodule less than 5 cm in diameter, or up to 3 nodules, with the largest being less than 3 cm in diameter, with no evidence of vascular invasion or distant metastasis) by using liver-directed therapy to provide a curative treatment.[4] Options for conducting downstaging include systemic therapy and locoregional therapies (LRTs). Moreover, the application of LRTs such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), transarterial radioembolization (TARE), stereotactic body radiation (SBRT), or a combination of therapies is more extensive.[5] TACE is the treatment approach most commonly used for unresectable HCC. Current guidelines including the Barcelona-Clinic Liver Cancer (BCLC) staging system recommend TACE as the standard treatment for intermediate-stage HCC. The effectiveness of TACE as an adjuvant therapy for HCC has been documented in clinical studies.[6]

TACE therapy, which is a selected local-regional strategy, can reduce tumor burden and may increase the success of further curative treatments, which improves survival rates in unresectable HCC patients. Although TACE is currently recommended as a first-line therapy for the treatment of intermediate-stage HCC, the incidence of recurrence is high, and the efficacy of TACE for unresectable HCC is discouraging.[7] Additionally, the factors that predict successful downstaging by TACE have not yet been clearly established. The aim of our study was to determine the factors that predict successful downstaging of HCC in patients outside the MC and provide theoretical support for increasing the efficacy of downstaging by TACE.[4]

Methods

Patients

We identified 101 patients with unresectable HCC who underwent initial TACE from October 2018 to June 2020 in the Affiliated Hospital of Southwest Medical University, and subsequently performed a retrospective cohort analysis. We included patients with HCC lesions outside the MC who were Child-Pugh class A-B, BCLC B-C, had good performance status, and had no evidence of tumor invasion into distant metastases. The inclusion of patients in our study was not restricted by the number of HCC lesions. Exclusion criteria were (1) patients with distant metastases; (2) unable to undergo TACE due to poor liver function (for example: advanced Child-Pugh class C, presence of refractory ascites, severe hepatic encephalopathy); (3) ECOG performance status greater than 1; (4) assessed without appropriate imaging diagnosis before initial TACE; (5) initial TACE for ruptured HCC; and (6) not followed up for at least one year. The diagnosis of HCC was made in accordance with American Association for the Study of Liver Diseases (AASLD) guidelines (contrast imaging showing an arterial hyperenhancement pattern with venous phase wash out or histological diagnosis after liver biopsy). These patients formed the derivation set of this study.

From July 2020 to October 2020, another cohort of 30 patients treated in the Affiliated Hospital of Southwest Medical University by TACE with the same selection criteria was analyzed as an independent external validation set. Successful downstaging was defined solely as the fulfilling of the MC following TACE. If there were more than 3 tumors, there should have been complete necrosis of treated HCC lesions, such that there were 3 or less viable tumors, with each tumor less than 3 cm to meet the MC. Downstaging was considered to have failed if there was 1 of the following: (1) progression of tumors as noted by an increase in the number or size of HCC lesions; (2) HCC lesions invading the hepatic or portal vessels; or (3) distant metastases. The protocol for the research project has been approved by Ethics Committee of the institution within which the work was undertaken (Acceptance number: SWMU-KY2021156). All persons gave their informed consent prior to their inclusion in the study.

Data collection

We recorded demographic data including age, sex, etiology of the liver disease, laboratory variables including hepatitis B surface antigen (HBsAg), white blood cell count, erythrocyte number, hemoglobin, platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, alanine aminotransferase (ALT), aspartate aminotransferase/transaminase (AST), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), lactate dehydrogenase (LHD), total bile acid (TBA), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), prealbumin (PA), total cholesterol (TC), carbamide, uric acid, creatinine, and tumor markers including α-fetoprotein (AFP), CA199, CA50, CA242, and CA724.

All laboratory values and tumor markers were determined 1 day before TACE. In addition, we recorded the tumor characteristics, such as the number of HCC lesions, the distribution of HCC lesions, and the longest diameter of HCC lesions.

Statistical analysis

In this study, the Kolmogorov-Smirnov method was used to test the normality of the continuous quantitative data in the sample. Quantitative data with normal distribution are expressed as the mean ± SD, quantitative data with non-normal distribution are expressed by interquartile range, and categorical data are shown as frequency and proportion. Student's *t* tests or nonparametric Wilcoxon rank-sum tests were used for quantitative data with normal distribution, and Pearson χ^2 tests were used for categorical factors. Bivariate analysis was performed using *t* tests, with successful downstaging as the outcome of interest to compare 2 groups.

Univariate logistic regression analysis was performed to identify variables that could predict successful downstaging. A P value of 0.05 or less was considered significant. The variables found to be significant in the univariate analysis, as well as variables thought to be clinically significant, were all included in the multivariate analysis. Logistic regression analysis was used for model development. Predictive accuracy and calibration of the model were performed using receiver operating characteristic (ROC) curves. All analyses were performed with SPSS version 25 software (IBM Corporation, Armonk, NY, USA

Results

Patient characteristics

In the derivation cohort (n = 101), the mean age was 57.43 ± 10.44, and 75.2% of patients were men. A total of 88.1% and 11.9% of patients were diagnosed at BCLC stage A and B, respectively. Conventional TACE (c-TACE) was performed in 57 patients, and drug-eluting beads-TACE (DEB-TACE) was used for 44 patients. A combination of molecular targeting drugs was used for 51 patients (50.5%). In terms of tumor factors, most patients had a single tumor (62.3%), and in 69 (68.4%) patients, the tumors were distributed in multiple lobes.

The clinical factors for the derivation (n = 101) and external (n = 30) validation sets prior to TACE are summarized in Table 1. There were no significant differences in baseline characteristics between the derivation and validation set.

Table 1
Baseline characteristics in patients between the derivation and validation set.

Variable	Derivation set (N = 101)	Validation set (N = 30)	P
Age, year	57.43 ± 10.44	57.23 ± 10.7	0.702
Gender			
Male	76 (75.2%)	23 (76.7%)	0.762
Female	25 (24.8%)	7 (23.3%)	
BCLC-stage			0.607
B	89 (88.1%)	26 (86.7%)	
C	12 (11.9%)	4 (13.3%)	
Number of tumors (cm)			0.951
3	63 (62.3%)	19 (63.3%)	
≥ 3	38 (37.7%)	89 (36.7%)	
PVTT-stage			0.887
0	81 (80.1%)	24 (80%)	
1	5 (4.9%)	1 (3.3%)	
2	10 (9.9%)	3 (10%)	
3	5 (5.1%)	2 (6.7%)	
Type of TACE			0.977
DEC-TACE	44 (43.5%)	13 (43.3%)	
C-TACE	57 (56.5%)	17 (56.7%)	
AFP (ng/ml)	113.11 (4.82–1000)	135.24 (5.17–1000)	0.512
Distribution of tumors			0.706
Single lobe	32 (31.6%)	10 (33.3%)	
Multiple lobe	69 (68.4%)	20 (66.7%)	
Child-stage			0.676
A	89 (88.1%)	26 (86.6%)	
B	12 (11.9%)	4 (13.4%)	
HBsAg (IU/ml)	920.89 ± 75.63	900.24 ± 80.40	0.744

Note: DEB-TACE=conventional TACE, DEB-TACE=drug-eluting beads, HBsAg=hepatitis B surface antigen, AFP=a-fetoprotein

Results of downstaging

Of the 101 patients in this study, 26 patients (25.7%) were successfully downstaged, and 75 patients (74.3%) failed downstaging. The distinction between the clinical and laboratory variables among patients who were successfully downstaged and those who failed downstaging is given in Table 2.

Table 2
Univariate and multivariate Logistic regression analyses to identify the variables associated with successful downstaging.

	Failure to downstage (N = 26)	Successful downstaging (N = 75)	OR (95% CI)	Adjusted OR (95% CI)	P value (adjusted OR)
Age, year	57.24 ± 11.86	57.67 ± 9.72	1.00 (0.96–1.04)	-	-
Gender					
Male	55	21	1[Reference]	-	-
Female	20	5	1.13 (0.44–2.92)	-	-
BCLC-stage					
B	63	25	1[Reference]	-	-
C	12	1	0.21 (0.26–1.70)	-	-
Number of tumors					
⩽3	40	23	1[Reference]	-	-
≥ 3	35	3	0.45 (0.24–0.78)	0.15(0.04–0.42)	0.018
Distribution of tumors					
Single lobe	49	21	1[Reference]	-	-
Multiple lobe	23	5	0.45 (0.15–1.32)	-	-
PVTT-stage					
No	20	23	1[Reference]	-	-
1	30	2	0.06 (0.01–0.27)	0.058 (0.008–0.264)	⩽0.001
2	25	1	0.04 (0.02–0.58)	0.035 (0.016–0.220)	⩽0.001
Type of TACE					
DEB-TACE	32	12	1[Reference]	-	-
C-TACE	45	14	0.87 (0.35–2.13)	-	-
Molecular targeting drug					
No	41	9	1[Reference]	-	-
Yes	34	17	2.28 (0.90–5.75)	-	-
Number of TACE treatments	2 (1–2)	2 (2–4)	0.45 (0.15–0.92)	-	-
Tumor diameter (cm)	8.3 (6.6–11.7)	6.3 (5.5–7.3)	0.67 (0.53–0.84)	0.56 (0.30–0.72)	0.021
HBsAg(IU/ml)	976.32 (35.84-2167.20)	9.06 (0.05-304.39)	0.74 (0.47–0.96)	0.90 (0.88–0.97)	0.014
WBC(10*9/L)	7.27 (6.04–10.08	5.75 (4.90–7.39)	0.68 (0.54–0.85)	-	-
RBC(10*12/L)	4.30 (3.87–4.70)	4.47 (4.09–5.02)	1.77 (0.97–3.20)	-	-
HGB(g/L)	129.49 ± 18.57	139.81 ± 16.20	1.03 (1.00-1.06)	-	-
PLT(10*9/L)	185.00 (121.00-252.00)	100.50 (70.00-177.25)	0.98 (0.97–0.99)	-	-
PT(s)	13.58 ± 1.37	12.83 ± 1.15	0.64 (0.44–0.92)	-	-
TT(s)	17.10 (16.20–18.00)	15.95 (14.60-17.12)	0.54 (0.37–0.79)	-	-
ALP(U/L)	123.80 (89.40-180.70)	88.15 (71.02-130.62)	0.98 (0.97–0.99)	-	-
ALT(U/L)	34.40 (24.14–71.10)	36.75 (28.27–67.60)	0.99 (0.99-1.00)	-	-
AST(U/L)	48.90 (32.40-193.60)	38.75 (31.67–71.70)	0.99 (0.99-1.00)	-	-
ALB(g/L)	38.55 ± 6.18	40.03 ± 4.42	1.04 (0.96–1.13)	-	-
TBA(umol/L)	8.25 (3.82–21.10)	6.00 (3.55–12.10)	0.98 (0.96–1.01)	-	-
TC(umol/L)	4.47 ± 0.96	4.46 ± 1.04	1.00 (0.59–1.67)	-	-
Urea(umol/L)	5.29 (4.30–6.77)	5.04 (4.29–6.43)	1.01 (0.79–1.29)	-	-
Creatinine(umol/L)	62.60 (51.70–71.90)	63.00 (56.92-71.00)	1.00 (0.98–1.02)	-	-

	Failure to downstage (N = 26)	Successful downstaging (N = 75)	OR (95% CI)	Adjusted OR (95% CI)	P value (adjusted OR)
Trioxypurine(umol/L)	341.40 (276.90-386.20)	335.75 (265.92-409.72)	1.00 (0.99-1.00)	-	-
AFP(ng/ml)	453.25 (2200.0-6664.4)	3.90 (5.06–26.81)	0.88 (0.67–0.99)	0.98 (0.99 – 0.97)	0.027
CA199(U/ml)	3.73 (2.28–13.77)	3.40 (2.55–5.85)	0.90 (0.84–1.24)	-	-

Predictors of successful downstaging

Multivariate analysis was performed for the factors that were used to predict successful downstaging of HCC outside the MC, and included the number of tumors (P = 0.018), portal vein tumor thrombosis (PVTT, P□0.001), the size of tumors (P = 0.021), hepatitis B surface antigen (HBsAg) (P = 0.014), and AFP (P = 0.027) as significant predictors of successful downstaging. Factors such as age, gender, the type of TACE, and laboratory variables such as total bilirubin and albumin, were not significant upon bivariate analysis. We used the risk factors obtained from the comparative analysis as independent variables, and performed logistic regression analysis. Then, we used a multiple nonlinear regression model to predict the efficiency of TACE. AFP, PVTT, the number and size of tumors, and HbsAg were used to construct the predictive equation:

Logit (P)=
$$11.261 - 0.013 * AFP - 3.108 * PVTT\,(1) - 2.742 * PVTT\,(2) + 2.117 * HBsAg - 2.397 * numberoftumor - 0.606 * \text{tumordiameter}$$

The predictive power of the predictive equation was evaluated by ROC curve analysis. The area under the ROC curve (AUROC) of the predictive equation was 0.908 (95% confidence interval, 0.832–0.957) (Fig. 1.).

Validation of the predictive model

For the purpose of externally validating this predictive equation, we collected data among a second set of patients (n = 30) undergoing TACE in the Affiliated Hospital of Southwest Medical University. The AUROC for the predictive equation was 0.863 (95% confidence interval, 0.721–0.959) (Fig. 2).

Discussion

TACE is the treatment approach most commonly used for unresectable HCC. The effectiveness of TACE as an adjuvant therapy for HCC has been documented in clinical studies. Downstaging therapy with TACE, as a selected local-regional strategy, reduces tumor burden to facilitate positive results from other types of treatments, which improves survival rates in unresectable HCC patients.[8] Another retrospective study showed that the 1-year, 2-year, and 3-year accumulating progression-free survival (PFS) rates were 68.8%, 40.6%, and 31.3%, respectively, after downstaging therapy by TACE; the 1-year, 2-year, and 3-year accumulating overall survival (OS) rates were 84.4%, 71.9%, and 53.1%, respectively, after downstaging therapy by TACE. Kaplan-Meier curves showed that successful downstaging was correlated with longer PFS and OS.[8] In related studies, after the initial TACE, 44 (25%) of 179 patients achieved tumor downstaging to within the MC.[9] However, to the best of our knowledge, no studies have been conducted to examine the factors affecting the efficacy of TACE on hepatocarcinoma downstaging.

A topic that remains controversial is the determination of which patients can benefit from TACE, and is related to the heterogeneity of the patients covered in the various studies and the diversity of the clinical elements influencing prognosis importance. In our retrospective study, we have attempted to try and determine the relevant factors affecting the efficacy of TACE on hepatocarcinoma downstaging.

In the current study, multivariate analysis indicated that AFP, PVTT, HBsAg, and the number of tumors and tumor diameter were the independent predictors of successful downstaging. Recently, several studies showed that AFP increased the predictive accuracy of post-liver transplantation (LT) survival in patients with HCC. Regarding downstaging of HCC in patients outside the MC, Yao at al. showed that an AFP□1000 ng/ml was a predictive factor of failed downstaging in a total of 122 HCC patients enrolled in a downstaging protocol consisting of LRT. Only 1 in 8 patients with an AFP greater than 1000 ng/ml were successfully downstaged in their study.[10] Similarly, in our study, only 5 of 44 patients with AFP levels higher than 1000 ng/ml were successfully downstaged, whereas 21 out of 57 patients with the AFP level lower than 1000 ng/ml were successfully downstaged. A previous study showed that AFP promotes the proliferation of HCC cells and the formation of tumor blood vessels, and it also enhances the antiapoptosis effect of cancer cells. 16 Thus, AFP plays an important role in the development and progression of HCC. This could be an explanation for our findings in the current study.

We also found that PVTT was an important predictive factor to evaluate the efficacy of downstaging by TACE. Patients with PVTT usually have an aggressive disease course, decreased liver function reserve, limited treatment options, higher recurrence rates after treatment, and therefore, worse OS. Among untreated HCC patients with PVTT, the reported median OS has been as low as 2 to 4 months. Many aspects of PVTT have impacted the theoretical and practical safety and efficacy of treatment, for example, disordered blood flow and associated impairment of liver function, heat-sink effects of the blood flow in the area of the PVTT, and tumor location in the blood vessel.[11] The presence of PVTT in patients with HCC has been consistently demonstrated by different series to be associated with poor prognoses, with a hazard ratio of death close to 2.[12] These data imply that PVTT may result in adverse effects that decrease the efficacy of downstaging.

In our study, HBsAg is a factor that can powerfully predict the efficacy of TACE. Recent studies suggested that pre-operative serum HBsAg levels □2000 S/CO are associated with high post-operative recurrence and poor prognosis.[13] In a previous study, Jing-Feng Liu et al. presented evidence that low pre- or post-operative levels of HBsAg may be associated with increased long-term survival in patients with hepatitis B virus (HBV)-related HCC. Patients with low pre-operative serum levels of HBsAg exhibited significantly higher OS than those with high serum levels at 1 year (90.5% vs 85.3%), 3 years (78.0% vs 70.6%), and

5 years (69.4% vs 52.6%; P = 0.002). [13] This poor prognosis is probably due in part to chronic HBV infection, which promotes not only recurrent HCC but also excessive inflammation and fibrosis in the liver that further reduces residual hepatic function.[13] Therefore, high HBsAg levels in serum may negatively affect the efficacy of downstaging.

In a previous study, Toso et al. showed that to establish a reliable selection policy by LRT, it is necessary to consider the size, number, or total tumor volume (TTV) of HCC.[14] In related studies, combining a variety of LRTs, TTV was noted to be an excellent independent predictor of successful downstaging. Arvind et al. indicated that for every 1 cm^3 increase in TTV, the odds of successful downstaging decreased by 2%. At a TTV cutoff of 200 cm^3, 76% of patients below this threshold were successfully downstaged, whereas only 4.5% of patients outside this threshold were successfully downstaged.[4]

Different studies showed that a large TTV can predispose a patient with AFP > 400 ng/ml. The AFP level has been linked with aggressive behavior of tumor cells and disease progression. Also, larger tumors were assumed to have a higher incidence of satellite nodules and vascular invasion. [15] Thus, the consequent relationship between larger TTV and the aggressive clinicopathological characteristics of HCC led to the valuable studies of the prognostic value of TTV.[15] Therefore, after performing a multivariate regression analysis, we proved that the number of tumors and tumor diameter can be used as predictors of downstaging efficacy by TACE.

We created a statistically predictive model based on a predictive logistic regression model tailored to the individual patient that provides accurate efficacy information regarding TACE in these patients. The model is simple and easy to use, integrating 5 predictors that constitute the essentials of preoperative clinical evaluation. The predictive performance of the model was further confirmed by an external validation set. The AUROC of the predictive equation was 0.908 (95% confidence interval, 0.832–0.957). The AUROC of the predictive equation by external validation set was 0.863 (95% confidence interval, 0.721–0.959).

Furthermore, the outcome of downstaging was not affected by age or gender in our study. The type of TACE did not influence the outcome of downstaging. Unexpectedly, molecular targeting drugs did not influence the outcome of downstaging in our study. A randomized phase III study conducted in Japan evaluated the effectiveness of sorafenib therapy when initiated after TACE. Four hundred and fifty-eight patients were randomized to either sorafenib or placebo, with a median time to randomization of 9.3 weeks. The study failed to show that the addition of sorafenib after TACE prolonged PFS and OS. (21) A recent article suggested that the arterial blood supply of the tumor may be associated with the efficacy of sorafenib. HCC tumors with an abundant arterial blood supply benefited more than those with a poor arterial supply.[16] The results in our study may be related to this factor. In addition, this suggests that the optimal timing and efficacy of molecular targeting drugs in relation to TACE have yet to be determined, which requires further studies.[17]

There were several limitations to the present study, and they include the small number of cases, the retrospective observational design of the study, and difficulty showing the small statistical significance. In this retrospective study, it was difficult to control confounding factors, leading to possible deviations in the results. However, based on the promising results, assessment of a larger number of cases, well-designed randomized controlled trials, and comparison with other locoregional therapies are essential to further propose the importance of TACE .

Conclusion

By combining 5 risk factors for pre-TACE, a novel, validated model was constructed for predicting the efficacy of TACE on downstaging. The results showed that the model exhibited satisfactory predictive performance. Thus, it is warranted that the model should be tested in prospective clinical trials.

Abbreviations

hepatocellular carcinoma
HCC, Milan criteria = MC, transarterial chemoembolization (TACE), DEB-TACE = conventional TACE, DEB-TACE = drug-eluting beads, HBsAg = hepatitis B surface antigen, portal vein tumor thrombi = PVTT, AFP = α-fetoprotein, locoregional therapies = LRTs, radiofrequency ablation = RFA, transarterial radioembolization = TARE, stereotactic body radiation = SBRT, WBC = white blood cell count, RBC = erythrocyte number, HGB = hemoglobin, PLT = platelet count, PT = prothrombin time, TT = thrombin time, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase/transaminase, ALB = albumin, TBA = total bile acid, TC = total cholesterol

Declarations

Ethics approval and consent to participate

The protocol for the research project has been approved by Clinical Trial Ethics Committee of affiliated Hospital of Southwest Medical University within which the work was undertaken (Acceptance number SWMU-KY2021156). All persons gave their informed consent prior to their inclusion in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors deny any conflicts of interest.

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Author's contributions

Song SU designed the study, Hao Min LIN, Fang Yi PENG and Bin HUANG and prepared first and final draft of the article; Yu GAN, Cheng FANG and Xiao Li YANG recorded the clinical and laboratory variables; Hao Min LIN performed multivariate logistic regression analyses to identify the variables associated with successful downstaging; Bo LI is senior author, Song SU is corresponding author, provided critical feedback and helped to modify manuscript.

# Hao Min LIN, Bin HUANG, Fang Yi PENG contributed equally.

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Figures

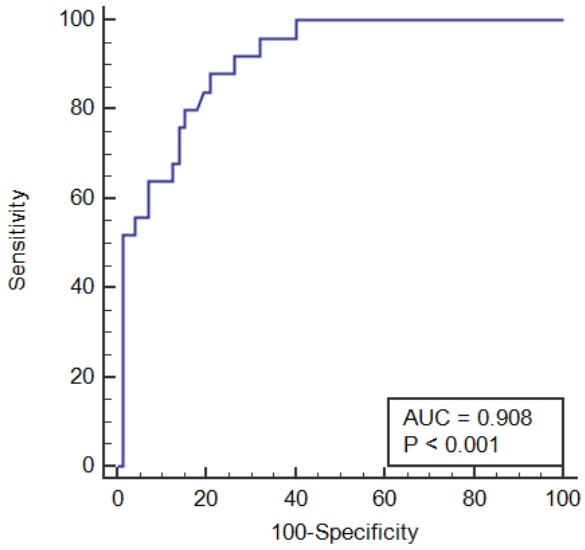

Figure 1

The area under the ROC curve (AUROC) of the predictive equation by the derivation set of this study.

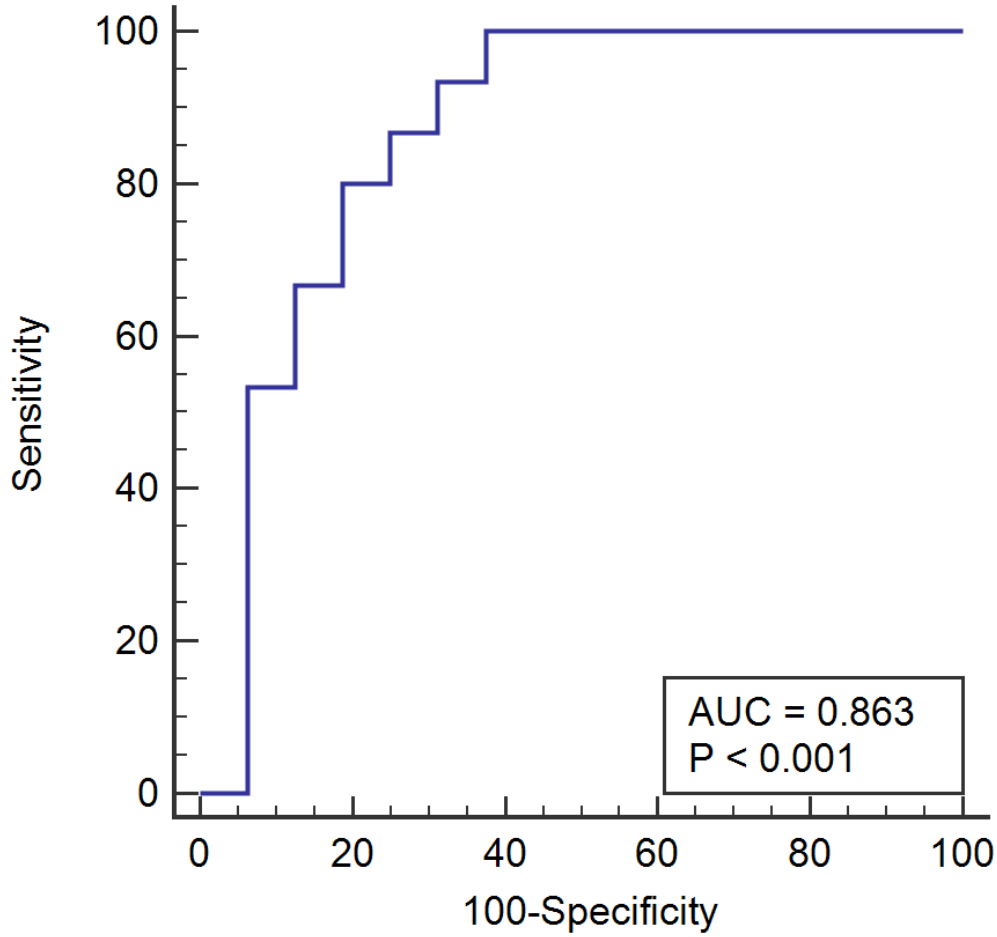

Figure 2

The area under the ROC curve (AUROC) of the predictive equation by the validation set of this study.